

# Exhibit O

8234739



# THE UNITED STATES OF AMERICA

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**United States Patent and Trademark Office**

April 25, 2022

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OF:**

**APPLICATION NUMBER: 15/705,172**

**FILING DATE: September 14, 2017**

**PATENT NUMBER: 9,994,851**

**ISSUE DATE: June 12, 2018**

**By Authority of the  
Under Secretary of Commerce for Intellectual Property  
and Director of the United States Patent and Trademark Office**



*W. Montgomery*  
**Wanda Montgomery**  
Certifying Officer



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/705,172	09/14/2017	Stephen Donald WILTON	AVN-008CN41	2879

123147 7590 10/05/2017  
Nelson Mullins Riley & Scarborough LLP/Sarepta  
One Post Office Square  
Boston, MA 02109

EXAMINER
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CHONG, KIMBERLY

ART UNIT	PAPER NUMBER
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1674

NOTIFICATION DATE	DELIVERY MODE
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10/05/2017

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com  
chris.schlauch@nelsonmullins.com  
ipqualityassuranceboston@nelsonmullins.com

**Office Action Summary**Application No.  
15/705,172Applicant(s)  
WILTON ET AL.Examiner  
KIMBERLY CHONGArt Unit  
1674AIA (First Inventor to File)  
Status  
No**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --****Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 09/26/2017.  
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims\***

- 5) ☒ Claim(s) 2 and 3 is/are pending in the application.  
 5a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 6) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 7) ☐ Claim(s) \_\_\_\_ is/are rejected.
- 8) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 9) ☒ Claim(s) 2 and 3 are subject to restriction and/or election requirement.

\* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see [http://www.uspto.gov/patents/init\\_events/pph/index.jsp](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).

**Application Papers**

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☒ The drawing(s) filed on 09/14/2017 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

- a) ☐ All b) ☐ Some\*\* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)  
 Paper No(s)/Mail Date 09/22/2017.
- 3) ☐ Interview Summary (PTO-413)  
 Paper No(s)/Mail Date. \_\_\_\_.
- 4) ☐ Other: \_\_\_\_.

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The present application is being examined under the pre-AIA first to invent provisions.

## **DETAILED ACTION**

### ***Status of Application/Amendment/Claims***

Claims 2 and 3 are pending and currently under examination.

### ***Information Disclosure Statement***

The submission of the Information Disclosure Statements on 09/22/2017 is in compliance with 37 CFR 1.97. The information disclosure statement has been considered by the examiner and signed copies have been placed in the file.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 2 and 3 are rejected under pre-AIA 35 U.S.C. 103(a) as being obvious over van Ommen (WO2004/083432 cited on IDS filed 09/22/2017) and Koenig et al. (Nature 338, 509 - 511 06 April 1989 cited on IDS filed 09/22/2017).

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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The claims are drawn to an antisense oligonucleotide of 20-31 bases comprising a base sequence 100% complementary to consecutive bases of exon 53 of the human dystrophin pre-mRNA, wherein the antisense oligonucleotide base sequence comprises at least 12 consecutive bases of SEQ ID NO: 195, wherein uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense induces exon 53 skipping. The claims are further drawn to a pharmaceutical composition comprising said antisense oligonucleotide.

van Ommen teach a genus of oligonucleotides 16-50 complementary to exon 53 and has identified an active range in the DMD gene and have shown two oligonucleotide h53AON1 and h53AON2 that cause skipping of exon 53 (see Table 2). van Ommen et al. teach the oligonucleotides can be complementary to the exon in the pre-mRNA. Thus given the sequence of the DMD gene has been identified, as demonstrated by Koenig et al., an oligonucleotide sequence complementary to that

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portion of the mRNA is exactly determined by the simple base pairing rules of DNA and RNA (G being complementary to C, and A being complementary to T (or U)).

vanOmmen et al. the oligonucleotide can have modifications such as morpholino phosphorodiamidate, peptide nucleic acid and locked nucleic acids, for example, and further teach the oligonucleotide comprises modified internucleoside linkages (see claim 12 and page 23). The oligonucleotide taught by van Ommen et al. encompasses both DNA and RNA nucleic acids as well as nucleic acids that are a combination of DNA and RNA as stated on page 9: lines 9-10 "Any oligonucleotide fulfilling the requirements of the invention may be used to induce exon skipping in the DMD gene." van Ommen et al. teach different nucleic acids may be used to generate the oligonucleotide (see page 9 line 30 - page 10). Thus oligonucleotides in which uracil bases are thymine bases are encompassed in the meaning of 'oligonucleotide' taught by van Ommen et al.

It would have been obvious to one of ordinary skill in the art to make an antisense oligonucleotide of 20-31 bases comprising at least 12 bases of SEQ ID No. 195. Given van Ommen et al. teach a genus of oligonucleotides of up to 50 nucleotides in length, one of skill in the art would have been motivated to use the sequence of h53AON1 to arrive at oligonucleotides of 20 nucleotides and having 12 nucleotides of SEQ ID No. 195 (which overlaps with 3 nucleotides of h53AON1). Because van Ommen et al. has identified exon 53 and shown oligonucleotides targeting this region can cause exon skipping and because the mRNA sequence containing the exon 53 was known in the prior art, as shown by Keonig et al., the combination of these teachings

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provides motivation to prepare obvious variants of h53AON1 to try and optimize the activity of the oligonucleotide to prepare the most effective therapeutic for treating DMD.

It would have been routine and a common strategy to try and enhance the oligonucleotide by identifying variants of that oligonucleotide that have a higher level of activity and a common and efficient strategy for doing so is to synthesize and test longer oligonucleotides containing within them the sequence known to have the desired activity.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP §

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717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit [www.uspto.gov/forms/](http://www.uspto.gov/forms/). The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to <http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp>.

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,455,636. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193.

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,232,384. Although the conflicting claims are not identical, they are not patentably

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distinct from each other because the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

#### **706.07(a) Final Rejection, When Proper on Second Action [R-07.2015]**

Second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p). Where information is submitted in an information disclosure statement during the period set forth in 37 CFR 1.97(c) with a fee, the examiner may use the information submitted, e.g., a printed publication or evidence of public use, and make the next Office action final whether or not the claims have been amended, provided that no other new ground of rejection which was not necessitated by amendment to the claims is introduced by the examiner. See MPEP § 609.04(b).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Kimberly Chong whose telephone number is 571-272-3111**. The examiner can normally be reached Monday thru Friday 9-5 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1674 Ram Shukla at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file

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folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/  
Primary Examiner  
Art Unit 1674

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: January 5, 2018  
Electronic Signature for Amy E. Mandragouras, Esq.: /Amy E. Mandragouras, Esq./

Docket No.: AVN-008CN41  
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:  
Stephen Donald Wilton *et al.*

Application No.: 15/705,172

Confirmation No.: 2879

Filed: September 14, 2017

Art Unit: 1674

For: ANTISENSE OLIGONUCLEOTIDES FOR  
INDUCING EXON SKIPPING AND  
METHODS OF USE THEREOF

Examiner: K. Chong

MS Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER**  
**37 C.F.R. § 1.111**

Dear Sir:

In response to the Office Action dated October 5, 2017 (Paper No. 20171001), please amend the above-identified U.S. patent application as follows:

The **Listing of the Claims** begins on page 2 of this paper.

**Remarks/Arguments** begin on page 3 of this paper.

Application No.: 15/705,172

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**LISTING OF THE CLAIMS**

1. **(Canceled)**
2. **(Previously Presented)** An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.
3. **(Previously Presented)** A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

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**REMARKS**

Claims 2 and 3 are pending in the application. Applicants respectfully request reconsideration and withdrawal of the rejections as discussed below. Should the Examiner agree, she is urged to call the undersigned to address any outstanding double patenting rejections to expedite prosecution of this application.

***Claim Rejections - 35 USC § 103***

Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being obvious over van Ommen *et al.* (WO 2004/083432) and Koenig *et al.* (Nature 338, 509 - 511 06 April 1989). Applicants respectfully traverse this rejection based on the following remarks.

**The Office failed to establish a prima facie case of obviousness**

The Office bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. (MPEP §2142, 9<sup>th</sup> Ed.) “The Federal Circuit has stated that ‘rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.’” (*Id.* citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); see also *KSR*, 550 U.S. at 418, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval).)

“Obviousness is a question of law with underlying factual findings, including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence such as commercial success, long-felt need, and the failure of others.” (*KSR Int’l Co. V. Teleflex, Inc.*, 550 U.S. 398 (2007) citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).) With respect to the third inquiry, to establish a *prima facie* case of obviousness, the Office must identify both a reason why a person of ordinary skill in the art would have combined the prior art elements to arrive at the claimed subject matter, and a reason why one of ordinary skill in the art would have considered the outcome predictable. (*KSR Int’l Co. V. Teleflex, Inc.*, 550 U.S. 398 (2007).)

“In cases involving the patentability of a new chemical compound, *prima facie* obviousness under the third *Graham* factor generally turns on the structural similarities and differences between the claimed compound and the prior art compounds.” According to

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established Federal Circuit precedent, a two-part "lead compound" analysis must be satisfied to establish a *prima facie* case of obviousness. (*Otsuka Pharmaceutical Co. Ltd., v. Sandoz, Inc.*, 678 F.3d 1280 (2012).) To satisfy the lead compound analysis, the Office must establish: (1) that one of ordinary skill in the art would have selected the asserted prior art compound as a lead compound for further development, and (2) that the prior art would have motivated one of ordinary skill in the art to modify the lead compound to make the claimed compound with a reasonable expectation of success. (*Id.* at 1291-1292.)

For the reasons below, neither prong of the two part inquiry has been met in the present case. The first prong is not met because the Office failed to provide a reason why one of ordinary skill in the art would have selected SEQ ID NO: 29 ("h53AON1") of van Ommen et al. as a lead compound. The second prong is not met because, even assuming that one of skill in the art would have selected h53AON1 as a lead compound, the Office failed to provide a reason or motivation to specifically *lengthen* h53AON1 by **nine** additional bases of SEQ ID NO: 195 to arrive at the limitation of claim 1 that the base sequence comprises at least 12 consecutive bases of SEQ ID NO: 195.<sup>1</sup> Moreover, there was a significant level of unpredictability associated with selecting a specific antisense oligonucleotide to induce effective exon skipping of human dystrophin pre-mRNA at the time of the invention, and therefore no reasonable expectation of success.

### Lead Compound Analysis

i. **The Office failed to provide a reason why a person of ordinary skill in the art would have selected h53AON1 as a lead compound**

A lead compound is "a compound in the prior art that would be most promising to modify in order to improve upon its...activity and obtain a compound with better activity." (*Otsuka Pharmaceutical Co. Ltd., v. Sandoz, Inc.*, at 1291 (citing *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)).) "[A] reason to select a compound as a lead compound depends on *more than just structural similarity*..." *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, 923 F.Supp.2d 602 at 657 (2013) (citing *Matrix Labs.*, 619 F.3d at 1354; emphasis added). Notably, it has been held that "absent

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<sup>1</sup> Applicants note and further explain below that, contrary to the position of the Office, the skilled artisan must lengthen h53AON1 by nine nucleotides, not two nucleotides, of SEQ ID NO: 195 to achieve the requirement of at least 12 bases of SEQ ID NO: 195 recited by the instant claims.

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a reason or motivation based on such prior art evidence, *mere structural similarity* between a prior art compound and the claimed compound *does not inform the lead compound selection.*" (*Otsuka Pharmaceutical Co. Ltd., v. Sandoz, Inc.*, at 1292 (citing *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010)); emphasis added.)

The Office has not provided any evidence or reasoning to support the conclusion that a person of ordinary skill in the art would have selected h53AON1 as the lead compound. Instead, the Office simply chooses it as its basis for the alleged obviousness of the claimed subject matter. Thus, its' selection by the Office in the absence of any supporting evidence or reasoning as a lead compound can only be through impermissible hindsight. Accordingly, the Office has not established that a person of ordinary skill in the art would select h53AON1 as the lead compound to modify to arrive at the claimed antisense oligonucleotides. For this reason alone, the claims are not *prima facie* obvious over the cited documents, and the Office should therefore withdraw the rejection.

ii. *The cited art does not motivate a person of ordinary skill in the art to modify h53AON1 to make the claimed antisense oligonucleotides with a reasonable expectation of success*

Even if the Office had established that a person of ordinary skill in the art would have selected h53AON1 as the lead compound, the second prong of the test also has not been met. The second prong of the lead compound analysis requires a determination of whether "the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound with a reasonable expectation of success." (*Otsuka Pharmaceutical Co. Ltd., v. Sandoz, Inc.*, 678 F.3d at 1292 (2012).)

The Office relies on van Ommen et al. as teaching a genus of oligonucleotides 16-50 bases in length that are complementary to, and cause skipping of, exon 53, and selects SEQ ID NO: 29 (h53AON1), which it contends is a 18-mer oligonucleotide having a sequence identical to three nucleotides of SEQ ID NO: 195. The Office contends, "[i]t would have been obvious for one of ordinary skill in the art to make an antisense oligonucleotide of 20-31 bases" using "the sequence of h53AON1 to arrive at an oligonucleotide of 20 nucleotides and having 12 nucleotides of SEQ ID No. 195. . ." by "preparing obvious variants of h53AON1 to try to optimize the activity of the oligonucleotide. . ." using "common and efficient strategies" such as

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synthesizing and testing “longer oligonucleotides containing within them” h53AON1. (See Office Action at pages 4-5 (emphasis added).)

Applicants submit that a person of ordinary skill in the art would not have been motivated to modify h53AON1 of van Ommen et al. to arrive at the claimed morpholino antisense oligonucleotides, and certainly not with a reasonable expectation of success. Notably, none of the cited documents would have motivated one of ordinary skill in the art to *increase the length* of the 18-mer h53AON1 to 27 bases 100% complementary to the exon 53 target region +23 to +69 and, let alone select at least 12 consecutive bases of SEQ ID NO: 195 and *thymine bases* in place of uracil bases, and select a *morpholino* chemistry backbone rather than a 2'-O-methyl phosphorothioate ("2'-O-Me-PS").<sup>2</sup>

Importantly, Applicants respectfully point out that the Office’s proposed strategy for modification of h53AON1 by lengthening it by only two bases would not result in an antisense oligonucleotide within the scope of the instant claims. To illustrate this point, Applicants provide the following alignment of h53AON1 (line 2) to SEQ ID NO: 195 (line 1).

1.	<u>CUGAAGGUGUUCUUGUACUUCAUCC</u>	SEQ ID NO: 195
2.	CUGUUGCCUCCGGUUC <u>UG</u>	h53AON1
3.	CUGUUGCCUCCGGUUC <u>CUGAA</u>	h53AON1+2 bases = 20mer
4.	CUGUUGCCUCCGGUUC <u>CUGAAGGUGUUC</u>	h53AON1+9 bases = 27mer

As can be seen from above and acknowledged by the Office, h53AON1 comprises only three consecutive bases of SEQ ID NO: 195 indicated in the underlined portion of lines 1 and 2. Addition of two additional consecutive bases to h53AON1 as proposed by the Office results in a 20mer that is within the claimed length range, but such a 20mer would only comprise five consecutive bases of SEQ ID NO: 195 as illustrated in line 3 – not at least 12 consecutive bases of SEQ ID NO: 195 as required by the claims. Applicants note that to achieve an antisense oligonucleotide of the instant claims comprising, *inter alia*, at least 12 bases of SEQ ID NO: 195, the skilled artisan would need to, *inter alia*, lengthen h53AON1 by 9 bases as illustrated in the underlined portion of line 4 above. Meaning, simply lengthening h53AON1 by two bases as suggested by the Office would clearly not result in the claim requirement of at least 12 bases of

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<sup>2</sup> Nor can it be found that the claimed invention would have been "obvious to try" as there are *not a "finite number of identified, predictable solutions"* such that one ordinarily skilled in the art could have pursued known potential solutions with a reasonable expectation of success. (*Examination Guidelines Update: Developments in the Obviousness Inquiry after KSR v. Teleflex*, issued by the United States Patent and Trademark Office (Federal Register, Vol. 75, No. 169: 53643, September 1, 2010); emphasis added.)

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SEQ ID NO: 195. Applicants base the remainder of the response based on modifying h53AON1 by, *inter alia*, adding 9 consecutive bases of SEQ ID NO: 195.

With regard to van Ommen et al., it cannot be said that there were a "finite number" of known, predictable solutions to the problem of designing a more efficient exon skipping antisense oligonucleotide with a reasonable expectation of success. In fact, van Ommen et al. suggest a wide variety of modifications to the antisense oligonucleotide structure with little specificity as to any individual oligonucleotide in the following:

[t]he complementary oligonucleotide generated through a method of the invention is preferably complementary to a consecutive part of between **16 and 50 nucleotides** of the exon RNA. **Different types of nucleic acid may be used** to generate the oligonucleotide. Preferably, the oligonucleotide comprises RNA, as RNA/RNA hybrids are very stable. Since one of the aims of the exon skipping technique is to direct splicing in subjects, it is preferred that the oligonucleotide RNA comprises a **modification providing the RNA with an additional property**, for instance, resistance to endonucleases and RNaseH, additional hybridization strength, increased stability (for instance, in a bodily fluid), increased or decreased flexibility, reduced toxicity, increased intracellular transport, and/or tissue-specificity, etc. Preferably, the modification comprises a 2'-O-methyl-phosphorothioate oligoribonucleotide modification.

With the advent of **nucleic acid-mimicking technology**, it has become possible to generate molecules that have a similar, preferably the same, hybridization characteristics, in kind, not necessarily in amount, as nucleic acid itself. Such equivalents are, of course, also part of the invention. **Examples of such mimics** equivalents are **peptide nucleic acid, locked nucleic acid and/or a morpholino phosphorodiamidate**. . . . **Hybrids between one or more of the equivalents among each other and/or together** with nucleic acid are, of course, also part of the invention. In a preferred embodiment, an equivalent comprises locked nucleic acid, as locked nucleic acid displays a higher target affinity and reduced toxicity and, therefore, shows a higher efficiency of exon skipping. (van Ommen et al. page 9, line 28 to page 11, line 2; emphasis added.)

van Ommen et al. also teach that "[i]t is thus not absolutely required that all the bases in the region of complementarity are capable of pairing with bases in the opposing strand... **[m]ismatches may to some extent be allowed**." (van Ommen et al. at page 3, ll. 3-8; emphasis added.) van Ommen et al. does not require that additional bases added to the antisense oligonucleotide be complementary to exon 53. *Id.*

Thus, there are a tremendous number of possible solutions to modify h53AON1 based on the length and position of "16-50 bases," mismatches, and many possible variations at any of three "substituents" (*i.e.*, nucleobase, ribose ring and phosphate linkage). Even if one focuses on

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the nucleobase sequence, assumes the chemical backbone and internucleotide linkages are unmodified, and limits the number of possible bases to those found in RNA, as shown in h53AON1, adding a single nucleobase to a 18-mer yields 8 possible sequence combinations (A, C, G, or U added before or after the 18-mer.)<sup>3</sup> Adding two nucleobases yields 64 possible combinations. Adding three nucleobases yields 256 combinations. Adding 9 nucleobases to obtain a 27-mer yields 2,621,440 possible combinations. And, adding 32 nucleobases to obtain a 50-mer yields 608,742,554,432,415,200,000 possible combinations.

Of course, this significantly *underestimates* the number of possible nucleobase combinations because van Ommen et al. specify "different types of nucleic acid," and is not limited to the "natural" bases A, C, G, and U found in RNA, but includes other naturally-occurring and non-naturally occurring nucleobases such as inosine, hypoxanthine, xanthine, and many others. Different types of nucleic acid also include nucleotide analogs and chemical modifications to the backbone, as all of the working examples by van Ommen et al. use 2'-O-Me-PS oligoribonucleotide modifications. Different types of nucleic acid also include "mimetics" such as peptide nucleic acids, locked nucleic acid, and morpholino phosphorodiamidates. (van Ommen et al. at page 10, ll. 11-16.) Given the incredibly large number of modifications to h53AON1 that are taught by the cited documents the only way to start from h53AON1 and modify it to arrive at the claimed antisense oligonucleotide is by the application of hindsight.

There is also no reason or motivation to specifically *increase* the length of h53AON1 as there is no teaching in van Ommen et al. with respect to the effects on exon skipping of *lengthening* (or shortening) an antisense oligonucleotide. In fact, as shown in Table 2, all of the antisense oligonucleotides with exon skipping activity are **15-24 bases in length**, and all but 3 of those are between **17 and 20 bases**, almost two thirds are either **19 or 20 bases**, and **none are 25 bases in length**. (van Ommen et al. Table 2 at page 48.) As the vast majority of the antisense oligonucleotides tested by van Ommen et al. in Table 2 are **20 bases or less** (25/30), one of ordinary skill in the art would have no reason or motivation to lengthen h53AON1 at all. In fact, one skilled in the art would be equally motivated to shorten h53AON1, as almost two thirds of

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<sup>3</sup> Assuming only the four RNA nucleobases, the number of nucleobase combinations for a particular length AON can be calculated by this formula, where "n" equals the number of bases being added to the chain:  $(4^n) \times (n+1)$ . This is because each additional nucleotide can be added to either end of SEQ ID NO: 29.

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the antisense oligonucleotides are either 19 or 20 bases, and the shortest antisense oligonucleotide with activity in Table 2 is 15 bases (h46AON4b).

Moreover, the Office failed to provide a reason why the skilled artisan would lengthen h53AON1. Instead, the Office merely concludes the skilled artisan would “prepare obvious variants of h53AON1 to try to optimize the activity of the oligonucleotide” and that the skilled artisan would “try” to enhance activity by “a common and efficient strategy” of synthesizing and testing “longer oligonucleotides containing within them the sequence known to have the desired activity.” Office Action at pages 4-5. The Office overlooks the fact that in Table 2 the only other antisense oligonucleotide made and tested by van Ommen et al. is h53AON2, and this antisense oligonucleotide – like h53AON1 – is an 18mer. Applicants respectfully point out that “[a] particular parameter must first be *recognized* as a *result-effective variable*, i.e., a variable which achieves a *recognized* result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation.” M.P.E.P. 2144.05(II)(B) (emphasis added); *see also In re Antonie*, 559 F.2d 618, 195 U.S.P.Q. 6 (CCPA 1977).

In the present case, the Office failed to satisfy its burden of providing evidence that oligonucleotide length was recognized in the prior art as a result effective variable for exon 53 skipping and activity in treatment for DMD. *See id.* Absent such evidence of recognition as a “result-effective variable[,]” it is not, therefore, routine optimization “within the skill of the artisan” to vary the length of an oligonucleotide to optimize exon 53 skipping and activity in the treatment of DMD. *See* M.P.E.P. 2144.05(II)(B); *In re Antonie*, 559 F.2d 618, 620, 195 U.S.P.Q. 6, 8-9 (C.C.P.A. 1977) (optimization of a parameter not recognized as a result-effective variable is an exception to the rule that “discovery of an optimum value of a variable in a known process is normally obvious”). Thus, the Office’s proffered rationale of routine optimization by lengthening h53AON1 does not apply.

Given the length of 16-50 bases and the many possible variations in nucleobase and backbone chemistry taught by van Ommen et al., there is *not* a “finite number” of known, predictable solutions to modifying h53AON1 such that one of ordinary skill in the art would arrive at the claimed morpholino antisense oligonucleotides of 20 to 31 bases having a base sequence 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), and having at least 12 consecutive bases of SEQ ID NO: 195 in which uracil bases are thymine bases, with a reasonable expectation of success. In fact, there is

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absolutely nothing in van Ommen et al. about selecting a morpholino chemistry backbone and thymine bases, rather than uracil bases.

*iii. High level of unpredictability in the field with no reasonable expectation of success*

Even assuming, *arguendo*, that one of ordinary skill would have selected h53AON1 of van Ommen et al. as a lead compound and would have been motivated to modify it in the particular way necessary to arrive at the subject matter of the claims, there would be no reasonable expectation of success because at the time the instant invention was made, there was a significant level of unpredictability associated with selecting specific antisense oligonucleotide sequences to induce effective dystrophin exon skipping. For example, the specification as originally filed notes that the size or length of an antisense oligonucleotide is not predictive of its efficacy (specification at page 21, lines 11-12). In addition, Applicants have found that there is no standard motif that can be blocked or masked by antisense molecules to redirect splicing (specification at page 21, lines 18-20). Applicants submit that the cited art does not provide sufficient guidance to arrive at the claimed subject matter considering the high level of unpredictability in the art.

Applicants refer the Office to van Deutekom *et al.* (2003) Nature Reviews, 4:774-783 (“van Deutekom Review”; submitted in an Information Disclosure Statement on September 22, 2017). This article is a review that generally discloses exon skipping in the dystrophin gene. The van Deutekom Review notes that interfering with exon selection for inclusion before splicing is “a process that is *not yet well understood*” (page 780, col. 1, lines 1-3, emphasis added).

Applicants also refer the Office to U.S. Patent Application Publication No. 2006/0147952 to van Ommen et al. (the ‘952 Publication) describe an approach in which “AONs were *empirically analyzed* for the induction of exon skipping.” (‘952 Publication at [0051]; emphasis added.) Such an approach relies on experience or observation and provides no indication as to what parameters are critical for the design of exon skipping antisense. As each antisense oligonucleotide must be empirically analyzed, the results are *unpredictable* as reported in Table 2 of the ‘952 Publication:

[t]heir different lengths and G/C contents (%) *did not correlate to their effectivity in exon skipping* (1, induced skipping, 2, no skipping). The AONs were directed to purine

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(A/G)-rich sequences as indicated by their (antisense) U/C content (%). Skipping of the target exons resulted in either an in-frame (IF) or out-of-frame (OF) transcript. (van Ommen et al. [0153], Table 2, footnote *a*; emphasis added.)

Additional evidence of unpredictability is found by analyzing the antisense sequences in Table 2 of the ‘952 Publication. For example, the two antisense oligonucleotides designed to induce skipping of exon 2 have overlapping nucleotide sequences:

h2AON1	cccauuuugugaauguuuucuuuu
h2AON2	uugugcauuuacccaauuugug

Despite the overlap in sequence, h2AON1 purportedly induced skipping, while h2AON2 did *not*. (‘952 Publication at Table 2.) And yet for another pair of overlapping AONs, both members of the pair did purportedly induce skipping:

h29AON1	uauccucugaaugucgcauc
h29AON2	gguauccucugaaugucgc

There is no explanation in the ‘952 Publication for these disparate results.

Much of the data in Table 2 of the ‘952 Publication was published in 2002 by Aartsma-Rus et al. (Neuromuscular Disorders, 12:S71-S77 (2002) (“Aartsma-Rus (2002)”); submitted in an Information Disclosure Statement on September 22, 2017). Aartsma-Rus (2002) discloses two specific oligonucleotides directed at dystrophin exon 53 and notes that there is *no correlation* between the length or sequence of the oligonucleotide and its effectiveness at inducing exon skipping. (Aartsma-Rus (2002) at page S76, col. 1, lines 43-45.) Still further, Aartsma-Rus (2002) teaches that *significant experimentation is required* to arrive at specific oligonucleotides, noting that “[w]e therefore have *no insight* into the actual position of the targeted sequence within the completely folded RNA structure. Its accessibility, and thus the effectivity of any designed AON, will therefore have to be tested *empirically* in the cells, as was done in this study.” (Aartsma-Rus (2002) at page S76, col. 1, lines 4-6; emphasis added.)

Another study, co-authored by one of the Applicants, examined skipping of exon 23 from the mouse DMD gene by RT-PCR following transfection with a series of overlapping 2’-Me-O-PS AONs, as shown in the following figure. Of the antisense oligonucleotides tested, only M23D(+12-13), M23D(+02-18), and M23D(-02-18) were effective in inducing detectable exon

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skipping. (Mann et al., J. Gene Med., 4(6): 644-654 (2002); submitted in an Information Disclosure Statement on September 22, 2017.)



(Mann et al. at 646.) Notably, the *shorter* antisense oligonucleotide M23D(-02-18), which is only *17 nucleotides* in length, was particularly efficient at inducing skipping and was reported to induce exon skipping at concentrations as low as 5 nM. The authors concluded that they could improve “the efficiency of the technique” by “*reduc[ing] the size* and the effective dose of the AO[N]s” examined. (Mann et al. at 644; emphasis added.)

Similar examples of unpredictability were reported by van Ommen et al. and other investigators at or near the date of Applicants' invention. In a 2005 publication the same design rationale described by van Ommen and coworkers was applied again. (Aartsma-Rus et al. Oligonucleotides, 15(4): 284-297 (2005) ("Aartsma-Rus (2005)"; submitted in an Information Disclosure Statement on September 22, 2017.) Table 1 of Aartsma-Rus (2005) provides the sequences of the antisense oligonucleotides and whether or not they induced skipping. (Aartsma-Rus (2005) at 285, first and second columns.) The following pairs of antisense oligonucleotides are found in the Table (+ and – refer to skipping ability):

h29AON10	guaguucccuccaacg	-
h29AON11	cauguaguucccucc	+
h43AON2	uuguuaacuuiuucccauu <sup>4</sup>	+

<sup>4</sup> There is a discrepancy between the disclosure of Aartsma-Rus (2005) and the sequence as shown by van Ommen et al. In the 2005 publication, the sequence is shown as uuguuaacuuiuucccauu, while in Table 2

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h43AON3	uguuaacuuuuucccauugg	-
h46AON8	gcuuuucuuuuaguugcugc	++
h46AON9	uuaguugcugcucuu	-
h48AON3	ggucuuuuauuugagcuuc	-
h48AON7	uuuauuugagcucaauuu	+

It is evident from these results that applying the design rationale described by van Ommen et al. is a hit-or-miss proposition in terms of whether any given antisense oligonucleotide will be capable of inducing skipping, *even in situations where the antisense oligonucleotides are very similar to each other in terms of nucleotide sequence, and other variables concerning the chemical backbone are fixed*. All of the antisense oligonucleotides described in the study “contain 2’-O-methyl RNA and full-length phosphorothioate (PS) backbones.” (Aartsma-Rus (2005) at 285.) None of the antisense oligonucleotides disclosed were longer than 24 nucleotides, and the majority of the antisense oligonucleotides were 20 nucleotides in length or shorter. (Aartsma-Rus at Table 1.) None of these antisense oligonucleotides include non-natural bases. Given the common chemical modifications of these antisense oligonucleotides, the data reported in this paper demonstrates the unpredictable impact that length and nucleotide composition make with respect to efficiency in inducing exon skipping.

The recognition of the lack of predictability in the field of exon skipping continued beyond 2005. A 2007 paper co-authored by van Ommen co-inventors Aartsma-Rus and van Deutekom states that “several years after the first attempts at dystrophin exon skipping with AOs [antisense oligonucleotides], *there are still no clear rules to guide investigators in their design*, and in mouse and human muscle cells *in vitro there is great variability for different targets and exons*.” (Arechavala-Gomez et al. Hum. Gene Ther., 18(9): 798-810, 807 (2007); submitted in an Information Disclosure Statement on September 22, 2017; emphasis added.)

And again in 2009 van Ommen and co-workers wrote that while existing software programs can facilitate design, “in general *a trial and error procedure* is still involved to

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of van Ommen et al. it shown as above having a sequence of "ccc" toward the 3’ end of the AON. It is assumed the latter is correct as it corresponds to the sequence of h43AON3.

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identify potent AONs.” (Aartsma-Rus et al., *Mol. Ther.*, 17(3):548-553 (2009) at 548; submitted in an Information Disclosure Statement on September 22, 2017; emphasis added.)

Evidence that selecting specific antisense oligonucleotide sequences to induce effective dystrophin exon skipping remains an unpredictable exercise is also found in a 2011 publication by Wu *et al.* (2011) *PLoS One*, 6(5): e19906 (submitted in an Information Disclosure Statement on September 22, 2017). Although Wu *et al.* is evidence developed after the instant filing date, the level of unpredictability in the art directly relates to whether the results obtained with any specific species would be unexpected and courts have held that it is not “improper to conduct additional experiments and provide later-obtained data in support of patent validity.” *Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). Evidence of the lack of predictability of in the field is relevant to the non-obviousness of the claimed antisense oligonucleotides over the cited art.

Wu *et al.* describe a systematic approach for identifying antisense oligonucleotides of high efficacy in inducing dystrophin exon skipping. Wu *et al.* designed 25 antisense oligonucleotides (AOs) to cover more than two thirds of exon 50 of the human dystrophin gene and the two flanking intron sequences. Wu *et al.* determined the efficiency of AO-induced skipping of exon 50 by comparing the activity of a series of AOs. Table 1 on page 4 of the publication summarizes all the AOs tested, including both 2'-O-methyl phosphorothioate and morpholino antisense oligonucleotides, as well as their reported activity in two assays. The exon skipping effect was determined using both a GFP reporter cell line with GFP expression coupled to exon 50 skipping and normal human myoblasts.

As shown in Table 1, Wu *et al.* tested AOs having a common 5' or 3' termini, but varied in length. Shown below is an excerpt from Table 1 of Wu *et al.*

hES0 AO2PS	-19-1	5'-CUUUAACAGAAAAGCAUAC-3'	19 bp	-	-	N/D
hES0 AO3PS	-19+1	5'-UCUUUAACAGAAAAGCAUAC-3'	20 bp	-	-	N/D
hES0 AO4PS	-19+3	5'-CCUCUUUAACAGAAAAGCAUAC-3'	22 bp	4%	3%	N/D
hES0 AO5PS	-19+8	5'-AACUCCUCUUUAACAGAAAAGCAUAC-3'	27 bp	21%	29%	N/D
hES0 AO6PS	-19+13	5'-CUUCUAACUCCUCUUUAACAGAAAAGCAUAC-3'	32 bp	3%	<1%	N/D

Each of these AOs target exon 50 starting at position (-19) and ending at position (-1), (+1), (+3), (+8) and (+13), respectively, and the oligonucleotides overlap at the 3' end. These AOs varied in length from 19 to 32 bases and the data shows that increasing AO length does not

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necessarily increase exon skipping activity and there is no reasonable expectation of success in increasing AO length to obtain increased exon skipping activity. For example, the 19- and 20-mer AOs hE50 AO2PS and hE50AO3PS were inactive. Increasing the length to 22 and 27 bases (hE50 AO4PS and hE50 AO5PS, respectively) resulted in increased activity, but a further increase to 32 bases (hE50 AO6PS) decreased activity significantly. Specifically, hE50 AO5PS is 5 nucleotides longer than hE50 AO4PS, but the level of GFP of hE50 AO5PS is 17% higher with respect to GFP assay and 26% higher with respect to human myoblasts. hE50 AO5PS is 5 nucleotides shorter than hE50 AO6PS, but the level of GFP of hE50 AO5PS is 18% higher with respect to GFP and 28% higher with respect to human myoblasts.

The data provided in Table 1 also demonstrate that when hE50 AO4PS (-19+3) was extended five nucleotides in length to hE50A AO5PS (-19+8), activity was increased. Notably, however, the addition of yet another five nucleotides to hE50 AO6PS (-19+13) essentially eliminated the activity.

In yet another example, a relatively short oligonucleotide (hE50 AO19PS; +97-5) at the 3' end of the exon showed low activity (3%) with respect to GFP, and activity did not increase when the oligonucleotide was lengthened by five or nine nucleotides at the 5' end (hE50 AO20PS and hE50 AO21PS, respectively) or by five nucleotides in the 3' direction (hE50 AO16PS). These four antisense oligonucleotides showed no activity in the human myoblasts. Thus, Wu *et al.* demonstrate that increasing or decreasing AO length results in unpredictable effects on exon skipping.

Importantly, the Patent Trial and Appeal Board (PTAB) in Interference No. 106,007 (“the ‘007 interference”) concerning exon 53 antisense oligonucleotides for DMD held that the field of antisense oligonucleotides for exon skipping for DMD was unpredictable at the time the instant application was filed. Its decision was based on the foregoing evidence and expert testimony. *See* Decision on Motions in Interference No. 106,007 (exon 53) dated May 12, 2016 (decision final upon withdrawal of CAFC Appeal No. 2016-2262; Decision on Motions previously submitted in an Information Disclosure Statement on September 22, 2017). Specifically, the PTAB determined that sequence length of antisense oligonucleotides that would maintain exon skipping was substantially unpredictable at the time US Application No. 11/233,495 was filed by Academisch Ziekenhuis Leiden (“AZL”). *See id.* at page 5, line 26 to page 6, line 3. Applicants note that the ‘495 application claims priority to the van Ommen *et al.* PCT application presently cited by the Office. In its Decision, the PTAB

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considered the foregoing evidence as representative of the state of the art with Exhibits 2010 and 2015 in Interference 106,007 corresponding to Aartsma-Rus and Wu *et al.*, submitted herewith as Appendices A and C, respectively. Unpredictability in this art was determined by the PTAB to have existed at the time of the instant invention (and years afterwards).

Upon consideration of this evidence, the PTAB stated “[t]he evidence indicates that at the time AZL filed its application, the identification of AONs that will cause exon skipping was generally thought to be unpredictable. One of the significant factors causing that unpredictability is the effect of the number of nucleobases present in the AON.” (Decision on Motions at page 17 (emphasis added)). In particular, the relationship between length of a base sequence and the ability of an antisense oligonucleotide to induce exon skipping was considered by the PTAB.

Despite the unpredictability in the art, the PTAB found obvious a 20mer AON based on SEQ ID NO: 193 over a completely overlapping 18mer (h53AON1). In this particular circumstance, the PTAB found that “a degree of exon skipping capability would likely be maintained due to a change in a *small number of complementary nucleobases* of an AON known to cause skipping” and, therefore, concluded “[i]t would have been obvious, for example, to add the *two* complementary nucleobases dictated by the known sequence of exon 53 to either end of h53AON1 with a reasonable expectation that the resultant 20 base AON would cause exon skipping.” *Id.* at pages 41-42 (emphasis added).

In contrast to the narrow issue considered by the PTAB described above, the PTAB does not support a determination of obviousness of the instant claims. The PTAB’s determination of unpredictability still applies. And to arrive at the instantly claimed antisense oligonucleotides, a person of ordinary skill would have to modify h53AON1 by adding at least *9 bases* (and would have to do so with a reasonable expectation of success). Such a modification in length cannot be said to be predictable under the Decision in the ‘007 interference. Accordingly, it would not have been obvious to extend h53AON1 by 9 bases at least because of the highly degree of unpredictability discussed above, and the Office failed to provide evidence to the contrary.

Furthermore, similar to the Office’s assertion, AZL argued that upon identification of h53AON1, “one skilled in the art would have investigated extended complementary sequences with the expectation that the longer sequences would bind and cause skipping.” *Id.* The PTAB did not find this argument persuasive at least because AZL failed to provide any

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evidence to support the basis for this expectation. *Id.* at page 18. Like AZL, the Office failed to provide evidence to support this argument. *See* Office Action at page 5. Accordingly, Applicants urge the Office to adopt the PTAB's determination of unpredictability in the field of exon skipping for DMD.

In summary, the van Deutekom Review, Aartsma-Rus and Wu *et al.* references, along with the Decision on Motions in the '007 interference, serve to illustrate the unpredictability associated with selecting *specific* antisense oligonucleotides that are effective for inducing skipping of dystrophin exons. Accordingly, the Office failed to establish a *prima facie* case of obviousness with respect to the predictability of the outcome in combining teachings of van Ommen *et al.* and Koenig *et al.* in the manner proposed to arrive at the claimed invention.

In view of the preceding remarks, Applicants submit that the Office failed to establish a *prima facie* case of obviousness based on the cited art. As such, Applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

#### ***Double Patenting***

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,455,636. Applicants respectfully traverse this rejection.

The Office asserts "the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193." Office Action at page 6. However, Applicants note the instant claims are drawn to antisense oligonucleotide having 20-31 bases and comprising at least 12 consecutive bases of SEQ ID NO: 195. Moreover, the '636 patent is directed to an antisense oligonucleotide comprising 20-50 bases and at least 20 consecutive bases of SEQ ID NO: 193. As such, Applicants point out that there is only a 2 base overlap between SEQ ID NOs: 193 of the '636 Patent and SEQ ID NO: 195 of the instant claims. Accordingly, Applicants respectfully request that the Office consider withdrawing the instant rejection in view of these facts and the foregoing remarks.

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,232,384. Applicants respectfully request clarification of this rejection. Specifically, The Office asserts

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“the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193.” Office Action at page 7. However, Applicants note the instant claims are drawn to antisense oligonucleotide having 21-30 bases and comprising at least 12 consecutive bases of SEQ ID NO: 195. Moreover, the ‘384 patent is directed to an antisense oligonucleotide *consisting* of SEQ ID NO: 195. Accordingly, Applicants respectfully request clarification.

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**CONCLUSION**

In view of the foregoing, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 217-4626. If a fee is due with this submission, please charge our Deposit Account No. 12-0080 under Order No. AVN-008CN41, from which the undersigned is authorized to draw

Dated: January 5, 2018

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15/705,172

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Stephen Donald WILTON

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UNITED STATES OF AMERICA

EXAMINER

CHONG, KIMBERLY

ART UNIT

PAPER NUMBER

1674

MAIL DATE

DELIVERY MODE

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary****Application No.**

15/705,172

**Applicant(s)**

WILTON et al.

**Examiner**

KIMBERLY CHONG

**Art Unit**

1674

**AIA Status**

No

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --****Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01/05/2018.  
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on \_\_\_\_.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims\***

- 5) ☒ Claim(s) 2-3 is/are pending in the application.  
5a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 6) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 7) ☒ Claim(s) 2-3 is/are rejected.
- 8) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 9) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement

\* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see [http://www.uspto.gov/patents/init\\_events/pph/index.jsp](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).

**Application Papers**

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

- a) ☐ All      b) ☐ Some\*\*      c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)  
Paper No(s)/Mail Date 01/05/2018.
- 3) ☒ Interview Summary (PTO-413)  
Paper No(s)/Mail Date 03/26/2018.
- 4) ☐ Other: \_\_\_\_.

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***Notice of Pre-AIA or AIA Status***

The present application is being examined under the pre-AIA first to invent provisions.

**DETAILED ACTION**

***Status of Application/Amendment/Claims***

Claims 2 and 3 are pending and currently under examination.

***Information Disclosure Statement***

The submission of the Information Disclosure Statements on 01/05/2018 is in compliance with 37 CFR 1.97. The information disclosure statement has been considered by the examiner and signed copies have been placed in the file.

***Response to Arguments***

***Claim Rejections - 35 USC § 103***

The rejection of claims 2 and 3 under pre-AIA 35 U.S.C. 103(a) as being obvious over van Ommen (WO2004/083432 cited on IDS filed 09/22/2017) and Koenig et al. (Nature 338, 509 - 511 06 April 1989 cited on IDS filed 09/22/2017) is withdrawn in response to Applicant's argument that one of skill in the art would not have been motivated to make the claimed oligonucleotide from h53AON1 taught by van Ommen.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

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F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit [www.uspto.gov/forms/](http://www.uspto.gov/forms/). The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to

<http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp>.

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The rejection of claims 2 and 3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,455,636 is withdrawn in response to Applicant's arguments.

The rejection of claims 2 and 3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,232,384 is maintained for the reasons of record.

Patent '384 are drawn to an antisense oligonucleotide targeted to annealing site H53A (+23+47) and consisting of SEQ ID No. 195 which is 25 nucleotides in length. The instant claims are drawn to an antisense oligonucleotide targeted to annealing site H53A (+23+47) having 20-31 bases comprising at least 12 consecutive bases of SEQ ID No. 195 but could also encompass 25 nucleotides of SEQ ID No. 195. Therefore the instant claims and the claims of the patent are not patentably distinct from each other.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KIMBERLY CHONG **whose telephone number is** (571)272-3111. The examiner can normally be reached Monday thru Friday 9-5 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1674 Ram Shukla at 571-272-07350735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/  
Primary Examiner  
Art Unit 1674